REMARKS

Applicants gratefully acknowledge the PTO's statement of allowability of method claims 9-15. No further amendments or remarks are directed to those claims. Applicants now introduce amendments to the buffer formulation claims, introduce additional buffer formulation claims, and present remarks in support of those claims.

The claimed invention includes buffer solutions useful for calibrating pH electrodes. The buffer formulation consists essentially of benzethonium chloride as bactericide, a buffering agent, sodium chloride, and water. It is important that the buffer formulation not include other substantive agents that might deteriorate or otherwise compromise the storage stability of the buffer formulation. As contemplated, these buffer solutions must be sterilized. During sterilization many components of conventional buffer formulations degrade to negatively affect the formulation, *e.g.,* change pH or produce a precipitate. *See, e.g., Specification, Table 3.* Thus, applicants have shown that the introduction of additional components would materially change the characteristics of applicants' invention. MPEP § 2111.03, *citing In re De Lajarte*, 337 F.2d 870 (CCPA 1964).

The claimed buffers are solutions (*Specification, ¶¶ 19 & 27*) that can be sterilized by gamma irradiation without substantially altering the pH and without producing any perceptible color, odor, or precipitate. *Specification, ¶ 24.* Moreover, the buffer solutions can be compounded and stored prior to sterilization for at least about 8 weeks without sustaining microorganism growth. *Specification, ¶ 25.*

Many of the composition claims now recite the more limiting transitional phrase "consisting essentially of", and so are restricted to those buffer formulations

containing substantial or effective amounts of only the recited components. It is applicants' intention that the recited components are the principal components of the formulation, but that other benign components might be included, deliberately or otherwise, in small or inconsequential amounts. That is, applicants contend that any substantial additional or alternative components are excluded by the recitation of "consisting essentially of."

Applicants' specification shows that the introduction of additional or alternative components, particularly other unclaimed bactericides, would materially change the characteristics of the buffer formulation. For example, applicants state that

> the introduction of a sterilization cycle to insure the sterility of the finished formulation can complicate the physicochemical profile of the sterilized product. Further, sterilization complicates the selection of a preservative since any such preservative must first be an effective biocide, but must also withstand the rigors of sterilization without affecting the pH, stability, cosmetics, or biocompatibility of the buffer.

Specification, ¶ 06; see also, ¶ 07 (discussing problems presented by use of phosphate buffers in medical devices).

Further, applicants have stated that the selection of benzethonium chloride, in particular, is important in the formulation of the claimed buffer solutions. *See, e.g., Specification, ¶ 12.* ("We examined a variety of preservatives for use in this buffer. While all were effective biocides pre-sterilization, many did not withstand a gamma sterilization cycle without negatively affecting the buffer integrity. *See* Table 3. Benzethonium chloride had minimal effect on the final buffer formulation with regard to pH level, stability, and cosmetic factors.")

Applicants show that the claimed combination of buffering agents and biocide is important for the end use contemplated. Likewise, the claimed properties are

essential to the utility of these buffer formulations, i.e., avoidance of byproducts causing substantial acidification or precipitation upon gamma irradiation, and prevention of microorganism growth prior to sterilization.

Those properties are important for the utility and function of the claimed formulations. For example, applicants state that phosphate buffered solutions are preferred calibration buffers but are excellent growth media for microorganisms. *Specification, ¶ 07.* Even short periods between buffer manufacture and product sterilization can lead to bioburden levels high enough to threaten the integrity of sterilization cycle. *Id.* Conventional calibration buffers often do not incorporate preservatives, but in the case of medical devices, buffer solutions must be aseptic. *Id.* Thus, applicants note, there is a need within the art for buffer formulations for pH measurement containing adequate biocide to inhibit microbial growth, while also being capable of withstanding the rigors of sterilization without affecting pH. *Id.*

Applicants' specification acknowledges the tension between the selection of buffers to maintain pH and the selection of biocides that withstand the rigors of sterilization. Applicants have found such a formulation with the combination of the claimed buffers and benzethonium chloride (with sodium chloride for isotonicity) in the absence of other agents that create sterilization byproducts that might destroy biocompatibility or otherwise materially affect pH.

Rejections Under 35 U.S.C. §102

Claims 1-3 and 7 stand rejected under §102.

Claim 7 stands rejected as anticipated by either of Miyazaki et al., USPN 5,308,849 and Miyazaki et al. USPN 5,438,060. Both the Miyazaki references are directed to, among other things, pharmaceutical formulations for reducing elevated

intraocular pressure. Neither of the Miyazaki references describes buffer formulations consisting essentially of the claimed components that both avoid substantial acidification (i.e., ≤ about 0.1 pH units (*Specification,* ¶25)) and produce no perceptible precipitate upon gamma irradiation. Likewise, nothing in the references teaches that those formulations prevent microorganism growth for eight weeks.

Both Miyazaki references require the presence of substantial additional components likely to produce sterilization byproducts. Miyazaki '060, Example 4, requires dipyridamole, potassium dihydrogen phosphate, disodium hydrogen phosphate $\bullet 12H_2O$, and 5N hydrochloric acid. Miyazaki '849, Formulation 6, requires Compound 1, a novel agent described as useful for the treatment of ocular hypertension and glaucoma. *See, e.g., column 1, lines 5-7.*

Additionally, Miyazaki '060 describes various examples of such formulations, all including dipyridamole, and wherein benzalkonium chloride is substituted, and presumably interchangeable with, benzethonium chloride. However, applicants plainly demonstrate that benzalkonium chloride produces a precipitate on gamma irradiation rendering it unsuitable as a buffer formulation for medical devices. *Specification, p. 6, Table 3.* Thus, neither of the Miyazaki references teaches the instant invention.

Claims 1-3 stand rejected under §102 as anticipated by JP 10-212220. The rejection asserts that the Abstract teaches a composition comprising 0.001-5 wt % of benzethonium chloride and sodium bicarbonate. The Abstract, and the reference itself, teach more than that. Both describe formulations requiring additional agents *e.g.,* a nonionic surfactant and/or an amphoteric surfactant; and, when necessary,

caking additives, humectants, abrasives, sweeteners, gelatin, titanium dioxide pigments. Thus, the reference teaches formulations that include substantial quantities of additional components excluded by the claims as amended. Accordingly, the reference fails to teach the claimed invention.

Claim 1 is rejected under §102(b) as anticipated by any one of JP 7-258050, Shore, Gaffar, or Chiang.

The rejection asserts that the English language abstract of JP 7-258050 teaches compositions comprising benzethonium chloride and sodium bicarbonate. However, the reference does not describe formulations such as those now claimed by Applicants. JP-258050 teaches that the formulations must include *granular* common salt and *granular* sodium bicarbonate, both having a specified average diameter. The Abstract does not recite the addition of water; and the reference as a whole describes tooth *paste* compositions. While the *paste* compositions of the examples describe addition of water, it is clear that they are not solutions, and further they comprise numerous additional agents excluded by the pending claims.

In contrast, the embodiments of claim 1 and its dependent claims are precipitate-free *solutions*. They are not anticipated by a mixture of *granular* salt and sodium bicarbonate, nor can they be anticipated by the multi-component tooth *paste* mixtures of the examples.

Further, the reference teaches that the various germicides (bactericides) are interchangeable. Applicants' specification shows that they are not (*Specification, Table 3*). Accordingly, one would be required to pick and choose among the disclosed formulations without any guidance as to which would produce a buffer solution having the claimed properties.

The reference also states that other agents, *e.g.*, a water-insoluble polishing agent and an oily ingredient or a water-soluble polymer are advantageously blended into the composition. Applicants have shown that the introduction of additional agents can have profound adverse effects not produced by the claimed formulations, and that those effects can render the formulations unsuitable to the intended purpose. Accordingly, the reference fails to teach the invention as claimed.

Shore, USPN 3,198,251 describes a deodorant preparation reportedly having a retarded tendency to cake having about 3 parts of water-soluble benzethonium quaternary salt to about 4 parts water soluble nitrate to about 1 part lactose; or those same three ingredients in about those same proportions and further including about 4 parts of water-soluble bicarbonate. As such, the disclosed preparations require various components excluded by the instant claims.

Further, the recited preparations are not likely to produce a solution that avoids substantial acidification or formation of a precipitate upon gamma irradiation, and/or prevents microorganism growth for at least about 8 weeks after formulation. Accordingly, the Shore '251 reference fails to teach the claimed invention.

Gaffar, USPN 4,370,314 describes an oral composition containing an antibacterial agent. The oral compositions described by Gaffar include the cited Example 1, a benzethonium chloride-containing mouthwash. Example 1 further includes: a flavor component, ethanol, Pluronic F-108, glycerin, sodium saccharin, sodium hexametaphosphate, and sodium bicarbonate. As such, the reference includes numerous components excluded by the instant claims. *See also* Example 3 (including benzethonium chloride and cetyl pyridinium chloride) and Example 4 (including benzethonium chloride and numerous agents as in Example 1).

Moreover, nothing in the reference teaches or suggests that such mouthwash preparations avoid substantial acidification or formation of a precipitate upon gamma irradiation, nor the prevention of microorganism growth for at least about 8 weeks. Further, one of ordinary skill in the art would not expect such properties from the formulation of Example 1. Accordingly, the Gaffar reference fails to teach the instant invention.

The Chiang reference, USPN 5,045,529, is directed to tonometric fluid for blood gas and co-oximetry instruments. The tonometric fluid described by Chiang is said to be a stable reference solution for calibrating and monitoring blood gas instrumentation. The solution includes an aqueous mixture containing a hemoglobin solution comprising at least about 95% reduced hemoglobin. Further, the only example including benzethonium chloride (Col. 6, lines 50 ff.) further includes bovine hemoglobin, 2-phenoxyethanol, sodium selenite, phytic acid, reduced glutathione, sodium bicarbonate, and HEPES. As such, the mixture includes numerous agents excluded by the instant claims, and thus does not anticipate the claims.

Further, nothing in the reference teaches that such mixtures avoid substantial acidification or formation of a precipitate upon gamma irradiation, nor that they prevent microorganism growth for at least about 8 weeks. Moreover, one of ordinary skill in the art would not expect that mixture to possess such properties. Accordingly, the Chiang reference fails to anticipate the claimed invention.

USPN 5,290,781 to Espino et al. is entitled "Ketane Serinol as an Agent to Reduce Intraocular Pressure." The reference states that the invention relates to the use of ketane serinol as an ophthalmic therapeutic agent to reduce intraocular pressure. The reference describes ketane serinol provided in an ophthalmic

therapeutic topical solution comprising ketane serinol, a non-ionic surfactant, a tonicity agent, a preservative, a stabilizing agent, a chelating agent, and a buffering system to control pH. While it is true that the preservative can be benzethonium chloride, and the buffering system can comprise potassium phosphates and/or sodium bicarbonate, the ophthalmic formulations require numerous agents excluded by the instant claims. Further those agents would be expected to give rise to precipitates and/or acidification upon gamma irradiation. Accordingly, the Espino reference does not anticipate the instant claims.

The Boctor et al. reference is entitled "Ultra-Pure Thrombin Preparation." Among other things, the Boctor reference describes a chromatography step that incorporates the use of sodium phosphate buffer and a bacteriostatic agent. The bacteriostatic agent is sodium azide. However, the reference asserts that sodium azide is not suitable when isolating thromboplastin, and suggests various bacteriostatic agents as alternatives. Recommended are: phenols, substituted phenols, chlorobutobenzyl alcohol, benzalkonium chloride, benzethonium chloride, thimerosal, and phenylmercuric nitrate. Notably, the reference does not actually describe the formulation of a buffer as claimed. Rather, it merely suggests that such a mixture of sodium phosphate and one of the bacteriostatic agents might be a suitable alternative to the recited chromatographic wash mixture when isolating thromboplastin. The reference thus invites one to select from among the listed bacteriostatic agents - many of which applicants have shown will not produce the claimed formulation - and then to use it in a column chromatography step for the purification of thromboplastin. As such, the reference does not anticipate the instant claims.

Rejections Under 37 C.F.R. 103(a)

Claims 4-6 stand rejected under §103(a) over JP10-212220. The rejection acknowledges that the reference does not teach the same concentration levels of buffering agents, but that it would have been obvious to modify those levels to arrive at the claimed invention. As stated above, this reference describes formulations requiring additional agents that are excluded by the amended claims. By teaching or suggesting that such agents must, or should be, included, the reference teaches away from the subject matter of both underlying claim 1 and of claims 4-6. That is, the reference fails to teach or suggest the underlying formulation of claim 1; and therefore cannot teach or suggest the formulation of claims dependent on claim 1, *i.e.*, claims 4-6.

Further, the rejection identifies nothing within the reference that teaches or suggests that the components of the claimed formulation could survive gamma irradiation without a decrease in pH and/or production of a precipitate. As such, the reference fails to provide any teaching or suggestion that would have motivated one to select the components of the claimed formulation, and to modify the concentrations of those components to arrive at the claimed formulations. Accordingly, the embodiments of claims 4-6 would not have been obvious in view of the cited reference.

Claim 8 stands rejected under §103(a) in view of either Miyazaki '849 or Miyazaki '060. The Miyazaki references fail to teach or suggest the subject matter of claim 8.

The '060 reference describes the formulation of eye drops in Example 4 that include benzethonium chloride among other agents including dipyridamole. The '849

reference similarly discloses an eye drop formulation comprising benzethonium chloride in combination with, among other agents, Compound 1, a polycyclic compound alleged to be effective for reducing elevated intraocular pressure.

Claim 8 now recites the transition phrase "consisting of." Both Miyazaki references describe mixtures that include components not recited in claim 8, which components are thus excluded by the language of the claim. As such, the reference does not teach or suggest the subject matter of claim 8.

Further, neither of those references describes a buffer solution consisting of the recited relative quantities of benzethonium chloride, a buffering agent, sodium chloride, and water. The rejection argues that, to the extent necessary to modify the disclosed formulations to arrive at the claimed formulations, it would have been routine optimization of a result-effective variable. But neither of the cited references is directed to the compounding of buffer formulations, much less buffer formulations having the recited properties of avoiding acidification and precipitation upon gamma irradiation. There is no guidance in either of those references regarding the preparation or use of a benzethonium chloride-containing buffer formulation, and there is no guidance as to how one might modify such formulations to achieve the characteristics now claimed by applicants.

Neither Miyazaki reference identifies benzethonium chloride as a bactericide that can effectively prevent substantial acidification and/or formation of precipitate upon gamma irradiation, nor the prevention of microorganism growth in the presence of a buffering agent. As there is nothing in either of the Miyazaki references describing or suggesting any of those properties, the reference does not provide the teaching to guide one of ordinary skill in the art how to "optimize" the concentration

of any of the common components, nor does it provide guidance as to the selection of the various components (including the exclusion of various components) to achieve the claimed buffer formulations. Accordingly, applicants respectfully submit that neither of the Miyazaki references teaches or suggests the invention of claim 8.

Conclusion

In view of the foregoing amendments and remarks, applicants respectfully request reconsideration and withdrawal of all outstanding rejections. Applicants submit that the claims are now in condition for allowance, and respectfully request formal notification to that effect. If, however, the Examiner perceives any impediments to such a notice of allowability, whether substantive or formal, the Examiner is encouraged to telephone Applicants' attorney at the number provided below. Such informal communication will expedite examination and disposition of this case.

Respectfully submitted,

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